

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/72865 A2

(51) International Patent Classification⁷: **A61K 38/00**

(21) International Application Number: **PCT/JP00/03340**

(22) International Filing Date: **24 May 2000 (24.05.2000)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
PQ 0663 **31 May 1999 (31.05.1999) AU**

(71) Applicant (for all designated States except US): **FUJISAWA PHARMACEUTICAL CO., LTD.** [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **IKEDA, Fumiaki** [JP/JP]; 5-1-11, Kisaichiyamate, Katano-shi, Osaka 576-0032 (JP). **OTOMO, Kazumi** [JP/JP]; 11-3, Funaki-cho, Ibaraki-shi, Osaka 567-0828 (JP). **WAKAI,**

Yosimi [JP/JP]; 3-14-21, Shonaisakaemachi, Toyonaka-shi, Osaka 561-0834 (JP). **MATSUMOTO, Satoru** [JP/JP]; 1-21, Sutokuin, Amagasaki-shi, Hyogo 660-0071 (JP).

(74) Agent: **TABUSHI, Eiji**; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP).

(81) Designated States (national): **JP, US.**

(84) Designated States (regional): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **ANTIFUNGAL COMBINATION USE**

(57) Abstract: There is described antifungal combination use of known antifungal agents such as the azoles or polyenes in combination with a lipopeptide compound antifungal agent. More particularly, the invention relates to antifungal combination use of azols such as fluconazole voriconazole, itraconazole, ketoconazole, miconazole, ER 30346 and SCH 56592; polyenes such as amphotericin B, nystatin, liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyoxins such as nikkomycins, in particular nikkomycin Z or nikkomycin X; other chitin inhibitors; elongation factor inhibitors such as sordarin and analogs thereof; mannan inhibitors such as predamycin, bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127; or complex carbohydrate antifungal agents such as CAN-296; with a lipopeptide compound (I) as described herein.

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International Bureau



(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/72865 A3

(51) International Patent Classification⁷: **A61K 38/12**,
A61P 31/10 // (A61K 38/12, 31:4196) (A61K 38/12,
31:7052)

Yosimi [JP/JP]; 3-14-21, Shonaisakaemachi, Toyonaka-shi, Osaka 561-0834 (JP). **MATSUMOTO**, Satoru [JP/JP]; 1-21, Sutokuin, Amagasaki-shi, Hyogo 660-0071 (JP).

(21) International Application Number: **PCT/JP00/03340**

(22) International Filing Date: **24 May 2000 (24.05.2000)**

(74) Agent: **TABUSHI**, Eiji; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP).

(25) Filing Language: **English**

(81) Designated States (*national*): **JP, US.**

(26) Publication Language: **English**

(30) Priority Data:
PQ 0663 **31 May 1999 (31.05.1999)** **AU**

(84) Designated States (*regional*): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

(71) Applicant (*for all designated States except US*): **FUJISAWA PHARMACEUTICAL CO., LTD.** [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

Published:
— *With international search report.*

(72) Inventors; and

(88) Date of publication of the international search report:
10 May 2001

(75) Inventors/Applicants (*for US only*): **IKEDA**, Fumiaki [JP/JP]; 5-1-11, Kisaichiyamate, Katano-shi, Osaka 576-0032 (JP). **OTOMO**, Kazumi [JP/JP]; 11-3, Funaki-cho, Ibaraki-shi, Osaka 567-0828 (JP). **WAKAI**,

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **ANTIFUNGAL COMBINATION USE**

(57) Abstract: There is described antifungal combination use of known antifungal agents such as the azoles or polyenes in combination with a lipopeptide compound antifungal agent. More particularly, the invention relates to antifungal combination use of azols such as fluconazole voriconazole, itraconazole, ketoconazole, miconazole, ER 30346 and SCH 56592; polyenes such as amphotericin B, nystatin, liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyoxins such as nikkomycins, in particular nikkomycin Z or nikkomycin X; other chitin inhibitors; elongation factor inhibitors such as sordarin and analogs thereof; mannan inhibitors such as predamycin, bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127; or complex carbohydrate antifungal agents such as CAN-296; with a lipopeptide compound (I) as described herein.

WO 00/72865 A3

PCT/JP00/03340

DOCKET NO.: 216008US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Fumiaki IKEDA, et al.
SERIAL NO.: NEW U.S. PCT APPLICATION
FILED: HEREWITH
INTERNATIONAL APPLICATION NO.: PCT/JP00/03340
INTERNATIONAL FILING DATE: May 24, 2000
FOR: ANTIFUNGAL COMBINATION USE

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119
AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

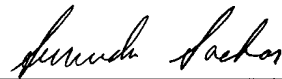
Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

<u>COUNTRY</u>	<u>APPLICATION NO</u>	<u>DAY/MONTH/YEAR</u>
Australia	PQ 0663	31 May 1999

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. **PCT/JP00/03340**. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,
OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618
Surinder Sachar
Registration No. 34,423



22850

(703) 413-3000
Fax No. (703) 413-2220
(OSMMN 1/97)

DOCKET NO.: 216008US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Fumiaki IKEDA, et al.

SERIAL NO.: NEW U.S. PCT APPLICATION

FILED: HEREWITH

INTERNATIONAL APPLICATION NO.: PCT/JP00/03340

INTERNATIONAL FILING DATE: May 24, 2000

FOR: ANTIFUNGAL COMBINATION USE

REQUEST FOR CONSIDERATION OF DOCUMENTS
CITED IN INTERNATIONAL SEARCH REPORT

Assistant Commissioner for Patents

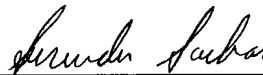
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that applicant(s) request that the Examiner consider the documents cited in the International Search Report according to MPEP §609 and so indicate by a statement in the first Office Action that the information has been considered. When the Form PCT/DO/EO/903 indicates both the search report and copies of the documents are present in the national stage file, there is no requirement for the applicant(s) to submit them (1156 O.G. 91 November 23, 1993).

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618
Surinder Sachar
Registration No. 34,423



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(703) 413-3000
Fax No. (703) 413-2220
(OSMMN 1/97)

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PW0-19742	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/JP 00/ 03340	International filing date (<i>day/month/year</i>) 24/05/2000	(Earliest) Priority Date (<i>day/month/year</i>) 31/05/1999
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/00/03340

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/12 A61P31/10 //(A61K38/12, 31:4196), (A61K38/12, 31:7052)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, PAJ, WPI Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 10782 A (FLATTERY AMY M ;MERCK & CO INC (US); ABRUZZO GEORGE K (US); BARTIZ) 19 March 1998 (1998-03-19)	1-9
Y	the whole document --- -/--	1-9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

28 November 2000

Date of mailing of the international search report

05/12/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Noë, V

INTERNATIONAL SEARCH REPORT

International Application No

PCT/90/03340

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>FRANZOT S P ET AL: "PNEUMOCANDIN L-743,872 ENHANCES THE ACTIVITIES OF AMPHOTERICIN B AND FLUCONAZOLE AGAINST CRYPTOCOCCUS NEOFORMANS IN VITRO" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, US, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, vol. 41, no. 2, 1 February 1997 (1997-02-01), pages 331-336, XP002051764 ISSN: 0066-4804 abstract page 332, column 1, last paragraph -page 333, column 1, paragraph 1 page 333, column 2, last paragraph page 335, column 1, last paragraph -column 2</p> <p>---</p>	1-9
X	<p>US 5 030 619 A (HECTOR RICHARD F) 9 July 1991 (1991-07-09) abstract column 1, line 55 -column 2, line 9 claims 1-9</p> <p>---</p>	1-3, 6-9
Y	<p>WO 96 11210 A (OHKI HIDENORI ;YAMADA AKIRA (JP); FUJISAWA PHARMACEUTICAL CO (JP);) 18 April 1996 (1996-04-18) cited in the application abstract page 1, line 17 -page 2, line 18 page 43, line 31 - line 34</p> <p>---</p>	1-9
A	<p>BARTIZAL K ET AL: "IN VITRO EVALUATION OF THE PNEUMOCANDIN ANTIFUNGAL AGENT L-733560, A NEW WATER-SOLUBLE HYBRID OF L-705589 AND L-731373" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, US, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, vol. 39, no. 5, 1 May 1995 (1995-05-01), pages 1070-1076, XP002051763 ISSN: 0066-4804 abstract page 1073, column 1, paragraph 2 page 1075, column 1, paragraph 3</p> <p>-----</p>	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/00/03340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9810782 A	19-03-1998	AU 721334 B	29-06-2000
		AU 4339297 A	02-04-1998
		CN 1235554 A	17-11-1999
		CZ 9900884 A	13-10-1999
		EP 0925070 A	30-06-1999
		JP 2000503675 T	28-03-2000
		NO 991207 A	11-05-1999
		PL 333282 A	22-11-1999
		SK 29999 A	14-02-2000
US 5030619 A	09-07-1991	NONE	
WO 9611210 A	18-04-1996	AU 696949 B	24-09-1998
		AU 3578095 A	02-05-1996
		BR 9504791 A	22-10-1996
		CA 2202058 A	18-04-1996
		CN 1168675 A	24-12-1997
		EP 0788511 A	13-08-1997
		FI 971397 A	27-05-1997
		HU 77736 A	28-07-1998
		JP 10324695 A	08-12-1998
		JP 2897427 B	31-05-1999
		JP 10507174 T	14-07-1998
		NO 971544 A	04-06-1997
		TR 960461 A	21-07-1996
		US 6107458 A	22-08-2000
		ZA 9508458 A	07-05-1996

PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

TABUSHI, Eiji
Fujisawa Pharmaceutical Co., Ltd.
Osaka Factory
1-6, Kashima 2-chome
Yodogawa-ku, Osaka-shi
Osaka 532-8514
JAPON

Date of mailing (day/month/year)

07 December 2000 (07.12.00)

Applicant's or agent's file reference

PWO-19742

IMPORTANT NOTICE

International application No.

PCT/JP00/03340

International filing date (day/month/year)

24 May 2000 (24.05.00)

Priority date (day/month/year)

31 May 1999 (31.05.99)

Applicant

FUJISAWA PHARMACEUTICAL CO., LTD. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

EP,JP

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 07 December 2000 (07.12.00) under No. WO 00/72865

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra

Telephone No. (41-22) 338.83.38



PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

TABUSHI, Eiji
Fujisawa Pharmaceutical Co., Ltd.
Osaka Factory
1-6, Kashima 2-chome
Yodogawa-ku, Osaka-shi
Osaka 532-8514
JAPON

Date of mailing (day/month/year) 17 July 2000 (17.07.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PWO-19742	
International application No. PCT/JP00/03340	
International publication date (day/month/year) Not yet published	
International filing date (day/month/year) 24 May 2000 (24.05.00)	Priority date (day/month/year) 31 May 1999 (31.05.99)
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
31 May 1999 (31.05.99)	PQ0663	AU	03 July 2000 (03.07.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Shinji IGARASHI

Telephone No. (41-22) 338.83.38



PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 21 February 2001 (21.02.01)	
International application No. PCT/JP00/03340	Applicant's or agent's file reference PWO-19742
International filing date (day/month/year) 24 May 2000 (24.05.00)	Priority date (day/month/year) 31 May 1999 (31.05.99)
Applicant IKEDA, Fumiaki et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
23 November 2000 (23.11.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Henrik Nyberg Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PWO-19742	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/JP00/03340	International filing date (day/month/year) 24/05/2000	Priority date (day/month/year) 31/05/1999
International Patent Classification (IPC) or national classification and IPC A61K38/00		
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 23/11/2000	Date of completion of this report 03.09.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Markopoulos, E Telephone No. +49 89 2399 8658



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JPO/03340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9810782 A	19-03-1998	AU 721334 B	29-06-2000
		AU 4339297 A	02-04-1998
		CN 1235554 A	17-11-1999
		CZ 9900884 A	13-10-1999
		EP 0925070 A	30-06-1999
		JP 2000503675 T	28-03-2000
		NO 991207 A	11-05-1999
		PL 333282 A	22-11-1999
		SK 29999 A	14-02-2000
US 5030619 A	09-07-1991	NONE	
WO 9611210 A	18-04-1996	AU 696949 B	24-09-1998
		AU 3578095 A	02-05-1996
		BR 9504791 A	22-10-1996
		CA 2202058 A	18-04-1996
		CN 1168675 A	24-12-1997
		EP 0788511 A	13-08-1997
		FI 971397 A	27-05-1997
		HU 77736 A	28-07-1998
		JP 10324695 A	08-12-1998
		JP 2897427 B	31-05-1999
		JP 10507174 T	14-07-1998
		NO 971544 A	04-06-1997
		TR 960461 A	21-07-1996
		US 6107458 A	22-08-2000
		ZA 9508458 A	07-05-1996

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP00/03340

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-15 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP00/0334C

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-7 in regard to industrial applicability.

because:

- ☒ the said international application, or the said claims Nos. 1-7 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-9
	No:	Claims -
Inventive step (IS)	Yes:	Claims -
	No:	Claims 1-9
Industrial applicability (IA)	Yes:	Claims 8, 9

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/JP00/03340

No: Claims -

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/JP00/03340

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-7 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

- D1: WO 98 10782 A (FLATTERY AMY M ;MERCK & CO INC (US); ABRUZZO GEORGE K (US); BARTIZ) 19 March 1998 (1998-03-19)
- D2: FRANZOT S P ET AL: 'PNEUMOCANDIN L-743,872 ENHANCES THE ACTIVITIES OF AMPHOTERICIN B AND FLUCONAZOLE AGAINST CRYPTOCOCCUS NEOFORMANS IN VITRO' ANTIMICROBIAL AGENTS AND CHEMOTHERAPY,US,AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, vol. 41, no. 2, 1 February 1997 (1997-02-01), pages 331- 336, XP002051764 ISSN: 0066-4804
- D3: US-A-5 030 619 (HECTOR RICHARD F) 9 July 1991 (1991-07-09)
- D4: WO 96 11210 A (OHKI HIDENORI ;YAMADA AKIRA (JP); FUJISAWA PHARMACEUTICAL CO (JP);) 18 April 1996 (1996-04-18) cited in the application

2. D1 claims an antifungal combination therapy using known antifungal agents such as the ones cited in the present application with a pneumocandin derivative (abstract; p. 1 - p. 3, l. 20) which is slightly different from the lipopeptide compound (I) of claim 1 of the present application.

D2 describes pneumocandin L-743,872 enhancing the activities of amphotericin B and fluconazole against C. neoformans whereby a marked synergism was observed in all combinations of amphotericin B. Combinations with fluconazole revealed different activities including synergism and additivity but no antagonistic interactions (abstract; p. 333, col. 2, par. 2 - p. 335, col. 2, par. 2).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/JP00/03340

In D3, a fungicidal composition comprising a nikkomycin (such as nikkomycin X and Z) and an echinocandin B known as cilofungin is claimed especially against aspergillosis (col. 1, l. 55 - col. 2, l. 10; claims 1-9).

D4 claims the cyclic hexapeptides cited in the present application (lipopeptide compound (I) in claim 1). Their antifungal activities e.g. against *Candida* and *Cryptococcus* (p. 43, l. 1-33) and their inhibitory activity on 1,3- β -D-glucan synthase is referred to (p. 1, l. 16-34).

Since the specific combination of lipopeptide compound (I) with the mentioned known antifungal agents such as azoles, polyenes and so forth for antifungal therapy is not cited in the prior art, claims 1-9 are considered as being novel (Art. 33(2) PCT).

3. Both D1 and D2 are considered to represent the closest prior art since both documents reveal a synergistic antifungal combination from which the subject-matter of claim 1 only differs in some minor changes in the lipopeptide compound (I).

The problem to be solved by the present invention may therefore be regarded as finding an alternative to the combinations of D1 and D2.

It is contemplated in D1 that other pneumocandin derivatives than the ones used would be useful in the combination therapy (p. 5, par. 1; p. 7, par. 2). Moreover, other studies have been carried out in order to test various pneumocandin derivatives in combination with amphotericin B and fluconazole.

Furthermore, it is known that the pneumocandins which are related to the echinocandins inhibit cell wall 1,3- β -D-glucan synthesis (e.g. D1: p. 3, par. 1). In D2, it is suggested that the relative resistance of *C. neoformans* to pneumocandins resulted from absence of 1,3- β -D-glucans in the cell wall of this yeast among other things. Hence, it is obvious that any inhibitor of 1,3- β -D-glucan synthesis will act antifungally if this 1,3- β -D-glucan is part of the cell wall of the yeast.

Since the synergistical action of lipopeptides such as the ones in D1, D2 and D3 with the antifungal agents cited in claim 1 of the present application is known and other lipopeptides are contemplated as acting in the same manner, the skilled in the art would be prompted to use the lipopeptides from D4 in combination, therefore the solution proposed in claims 1-9 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/JP00/03340

4. For the assessment of the present claims 1-7 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PW0-19742	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/JP 00/03340	International filing date (day/month/year) 24/05/2000	(Earliest) Priority Date (day/month/year) 31/05/1999
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/00/03340

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/12 A61P31/10 //(A61K38/12,31:4196),(A61K38/12,31:7052)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, PAJ, WPI Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 10782 A (FLATTERY AMY M ;MERCK & CO INC (US); ABRUZZO GEORGE K (US); BARTIZ) 19 March 1998 (1998-03-19)	1-9
Y	the whole document --- -/--	1-9

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

28 November 2000

Date of mailing of the international search report

05/12/2000

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Noë, V

INTERNATIONAL SEARCH REPORT

Intern. Patent Application No.

PCT/JP90/03340

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>FRANZOT S P ET AL: "PNEUMOCANDIN L-743,872 ENHANCES THE ACTIVITIES OF AMPHOTERICIN B AND FLUCONAZOLE AGAINST CRYPTOCOCCUS NEOFORMANS IN VITRO" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, US, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, vol. 41, no. 2, 1 February 1997 (1997-02-01), pages 331-336, XP002051764 ISSN: 0066-4804 abstract page 332, column 1, last paragraph -page 333, column 1, paragraph 1 page 333, column 2, last paragraph page 335, column 1, last paragraph -column 2</p> <p>---</p>	1-9
X	<p>US 5 030 619 A (HECTOR RICHARD F) 9 July 1991 (1991-07-09) abstract column 1, line 55 -column 2, line 9 claims 1-9</p> <p>---</p>	1-3, 6-9
Y	<p>WO 96 11210 A (OHKI HIDENORI ;YAMADA AKIRA (JP); FUJISAWA PHARMACEUTICAL CO (JP);) 18 April 1996 (1996-04-18) cited in the application abstract page 1, line 17 -page 2, line 18 page 43, line 31 - line 34</p> <p>---</p>	1-9
A	<p>BARTIZAL K ET AL: "IN VITRO EVALUATION OF THE PNEUMOCANDIN ANTIFUNGAL AGENT L-733560, A NEW WATER-SOLUBLE HYBRID OF L-705589 AND L-731373" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, US, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, vol. 39, no. 5, 1 May 1995 (1995-05-01), pages 1070-1076, XP002051763 ISSN: 0066-4804 abstract page 1073, column 1, paragraph 2 page 1075, column 1, paragraph 3</p> <p>-----</p>	1-9